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Catalytic Nanomedicine: Antioxidant Action and Clinical Benefits Using Cerium Oxide Nanoparticles

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ABSTRACT

Oxidative stress plays a central role in the pathogenesis of various chronic diseases by driving inflammation, cellular damage, and metabolic dysfunction. The imbalance between reactive oxygen species (ROS) production and antioxidant defenses contributes to neurodegenerative, cardiovascular, and inflammatory disorders, highlighting the urgent need for innovative therapeutic strategies. In this context, catalytic nanomedicine has emerged as a promising approach to mitigate oxidative damage through nanocatalysts that mimic enzymatic antioxidant activity. This review explores recent advances in antioxidant nanocatalysts, particularly metal oxide nanoparticles such as cerium oxide, emphasizing their biochemical mechanisms, therapeutic applications, and potential for clinical translation. This nanomaterial has demonstrated the ability to modulate redox homeostasis, reduce inflammatory markers, and preserve cellular integrity in preclinical models. Moreover, multifunctional nanocatalysts offer advantages such as enhanced stability, tunable catalytic activity, and the potential for targeted delivery, making them compelling candidates for precision medicine. However, despite their potential, significant challenges remain, particularly concerning biocompatibility, long-term safety, and large-scale production. Further research is needed to optimize physicochemical properties, improve bioavailability, and ensure regulatory compliance. Therefore, addressing these limitations is essential to accelerate the translation of experimental findings into clinical practice, paving the way for advanced nano-therapies with extensive biomedical applications that utilize catalytic mechanisms to modulate redox balance.

Keywords: Catalytic nanomedicine, Oxidative stress, Antioxidant nanocatalyst, Reactive Oxygen Species (ROS), Cerium oxide nanoparticles

Purpose, Rationale, and Limitations

In this review, the goal is to critically evaluate the fundamental principles and recent advances in catalytic nanomedicine, focusing on metal oxide nanoparticles, particularly in their nano form, such as cerium and iron oxides, which exhibit enzyme-like activities (e.g., mimicking superoxide dismutase and catalase). The rationale for this investigation stems from the unique physicochemical characteristics of these nanomaterials, including their high surface-to-volume ratio, redox cycling capabilities (e.g., the Ce^{3+}/Ce^{4+} interconversion), and ease of surface functionalization. Together, these properties offer a more targeted and effective approach to modulating redox processes compared to conventional antioxidant therapies. However, several limitations currently hinder the clinical translation of these promising ceria nanocatalysts. These challenges include achieving reproducible and scalable synthesis methods that produce nanoparticles with controlled size, morphology, and surface properties, ensuring long-term biocompatibility and minimal toxicity, and addressing complex issues related to biodistribution, clearance, and potential off-target effects in vivo.

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Introduction

Catalytic nanomedicine, a new field at the boundary between nanotechnology and biochemistry, uses catalytic nanoparticles, also known as nanocatalysts, to mimic and amplify the activity of enzymes, mainly in the neutralization of Reactive Oxygen Species (ROS). That is, it drives selective and exact redox reactions that help maintain oxidative homeostasis and modulate inflammation. Oxidative stress represents an imbalance between the production of ROS and antioxidant capacity in organisms, leading to damage in lipids, proteins, and nucleic acids, thus being associated with the progression of diseases like cancer, cardiovascular diseases, neurodegenerative disorders, and inflammatory diseases [1]. Therefore, neutralizing ROS becomes an important therapeutic target in treating these disorders [2-5], a fact-finding increasing inroads in biomedical science. Thus, based on a systematic approach and considering the literature on PubMed, Scopus, and Web of Science database, this review aims to describe some basic concepts of catalytic nanomedicine and some examples and applications of nanoparticles of metal oxides, emphasizing metal oxides in nano form. This article covers the basics of this revolutionary technology, addressing advances in developing antioxidant nanocatalysts, including cerium and iron oxide nanoparticles, and their therapeutic applications and clinical implications [6-8]. Perspectives and challenges associated with using these materials are also presented, highlighting the obstacles that must still be overcome for the technology to find wide application in treating oxidative stress-related diseases.

Discussion

Basics of Catalytic Nanomedicine

Nanotechnology is the understanding and control of matter at nanoscale dimensions between approximately 1–100 nm, where unique phenomena enable novel properties and applications. These properties may differ in important ways from the properties of bulk materials and single atoms or molecules. New medical breakthroughs include advanced biomedical research tools, standards for experiments and diagnostic tests, the study of DNA and its component genes, bone implants, and other related treatments. Nanomedicine is an interdisciplinary field that investigates materials at the nanometer scale (≤100 nm) for the diagnosis, therapy, and prevention of diseases, exploiting the unique properties acquired at this scale, including higher surface reactivity, quantum effects, and more efficient biological interactions [9]. These attributes allow nanoparticles to interact directly with cellular and molecular structures, such as plasma membranes, organelles, and proteins, enhancing the precision and efficacy of therapeutic interventions to an unprecedented level [10]. For a comparison of the size of atomic and molecular particles with DNA, proteins, and viruses, we can affirm that one nanometer is still large compared to the atomic scale. An atom has a diameter of about 0.1 nm, and the nucleus of an atom is much smaller - about 0.00001 nm. In general, DNA, proteins, and some viruses have size in the nanoscale (from 1 to 100 nm), evidencing that catalytic nanomedicine research may be effective in this range.

In this application of catalytic nanomedicine or nanocatalysis, the underlying concept is based on using nanoparticles or nanomaterials as artificial catalysts, all capable of inducing chemical reactions in a controlled and highly efficient manner within biological systems [11]. In conventional catalysis, this involves chemicals that increase the rate of chemical reactions by lowering the activation energy needed without being consumed by the response [12]. At the nanoscale, catalysts have improved properties, such as direct interactions between the nanoparticle surface and the reagents in the biological microenvironment [13]. The high specific surface area of these particles increases their catalytic activity (since it enhances the existence of many active sites for chemical reactions). In contrast, properties like size, shape, composition, and surface functionalization of the nanoparticles are tuned to achieve optimal selectivity and efficiency [14,15]. This precision enables the transformation of substrates into desired products, the regulation of chemical microenvironments, and the induction of specific biological responses. The surface functionalization of nanoparticles, generally by adding bioactive ligands, is essential to ensure that these interactions will preferably occur at target sites or tissues, contributing to the minimization of collateral damage and the efficiency of treatment.

Antioxidant Effects and Clinical Benefits

Cellular Protection Against Oxidative Damage

Neutralizing ROS is one of the most important mechanisms for safeguarding cellular homeostasis and preserving vital biomolecular structures. These ROS, natural by-products of cellular metabolism and especially mitochondrial processes, may accumulate in excess and lead to a pathological condition known as oxidative stress [16]. This condition arises from the oxidative degradation of lipids, proteins, and nucleic acids and compromises cellular integrity and functionality. Lipids undergo lipid peroxidation, compromising cellular membranes' fluidity, selective permeability, and stability. The oxidative modifications of proteins alter enzymatic activity, cell signaling, and molecular interactions. DNA attacks result in strand breaks, adduct formation, and changes in nitrogenous bases, promoting genotoxic mutations that lead to chronic diseases [17].

In this regard, iron oxide and cerium oxide nanoparticles are considered potential therapeutic agents in medicine because of their ability to catalyze antioxidant reactions like enzymes, including superoxide dismutase (SOD) and catalase [18,19]. They decompose superoxide anion (O_2•−) and hydrogen peroxide (H_2O_2), forming less reactive molecules: oxygen (O_2) and water (H_2O). Therefore, this inhibits the formation of hydroxyl radicals (OH•), highly reactive intermediates that amplify oxidative stress. Besides, cerium oxide nanoparticles hold some unusual redox properties by themselves; their surface is made of Ce^{3+} and Ce^{4+} cations, which provide continuous regenerative cycling between oxidation states and, therefore, amplify and prolong their antioxidant action in the cellular microenvironment [20].

Preclinical studies have shown that antioxidant nanoparticles reduce malondialdehyde levels, a lipid peroxidation marker, in rats' brains and protect against DNA strand breaks and genomic instability [21]. In the clinical setting, they could prevent ischemic injuries, reduce oxidative stress in neuronal tissues, and exert cardioprotection in reperfusion models. All these findings point to their therapeutic potential in various chronic diseases related to oxidative stress and promising prospects in oncology, neurology, and cardiology.

Modulation of the Inflammatory Response Through Antioxidants

The interaction between oxidative stress and inflammation creates an intrinsic relationship that makes antioxidant nanocatalysts promising tools for regulating inflammatory processes. Apart from initiation, oxidative stress also amplifies inflammatory responses through the activation of redox-modulated intracellular pathways, including NF-κB (nuclear factor kappa B) and MAPK (mitogen-activated protein kinase) [22,23]. These lead to the production of pro-inflammatory cytokines, such as TNF-α **(**Tumor Necrosis Factor-alpha) and IL-6 **(**Interleukin-6)**,** which sustain the state of inflammation and further promote structural tissue damage.

Thus, nanocatalysts serve as efficient neutralizers of ROS; they remarkably reduce the activation of intracellular sensors associated with oxidative stress. The most important are NLRP3 (NOD-like receptor pyrin domain-containing protein 3) inflammasomes, which lead to the production of inflammatory cytokines such as IL-1β (Interleukin-1 beta) [24].

The critical role played, in this context, by nanoparticles (for example, cerium oxide and manganese oxide) is performed with the imitation of the antioxidant enzymes of decomposition by promoting superoxide and hydrogen peroxide before causing radical damage in a cell [25,26]. This antioxidant breaks the cycle in which ROS causes oxidative damage and amplifies inflammatory processes. Inflammation, therefore, increases the ROS levels, sustaining this imbalance. Thus, the restoration of redox balance by nanocatalysts disrupts this cycle and creates a favorable environment for tissue recovery and remodeling of the inflammatory milieu [27].

More than just antioxidant actions, nanocatalysts affect macrophage polarization, which lies at the very center of the orchestration of the inflammatory response. Under oxidative stress, macrophages are polarized toward the M1 phenotype, which sustains inflammation. The protective action of nanocatalysts redirects these cells toward the M2 phenotype, characterized by promoting inflammatory resolution and tissue repair [28]. These features show that nanocatalysts do much more than just mitigate oxidative stress; they act holistically to break the

chains of inflammation. They, therefore, represent new therapeutic strategies with possible applications in chronic inflammatory diseases such as rheumatoid arthritis, cardiovascular disorders, and metabolic syndromes [29].

Maintaining Vascular Function

The inner layer of blood vessels, the vascular endothelium, has a critical role in maintaining vascular homeostasis, regulating several processes, including vasodilation, selective permeability, angiogenesis, and inflammatory responses. Still, its susceptibility to oxidative stress due to ROS accumulation renders it prone to functional and structural alterations [30]. One of the significant targets of oxidative stress in the endothelium is nitric oxide, a crucial vasoactive molecule responsible for relaxing vascular smooth muscle and regulating vascular tone. The reaction of ROS with nitric oxide (NO) gives way to peroxynitrite ($ONOO^-$), a reactive nitrogen species that reduces the bioavailability of NO and causes oxidative damage to endothelium. Consequently, there is a loss in the ability of NO to cause vasodilation; hence, the endothelium becomes unable to respond to physiological and pathological stimuli [31].

In this context, nanocatalysts, especially CeO_2 nanoparticles, play a protective role by virtue of their antioxidant action that allows the catalytic decomposition of ROS, preventing peroxynitrite formation. Saving the functionality of NO, these nanoparticles preserve the ability of the endothelium to act as a mediator of vasodilation and to protect the cellular components from oxidative damage [32].

Another related aspect is their contribution to endothelial repair. Under conditions of oxidative stress, the endothelium expresses increased levels of adhesion molecules such as ICAM-1 (Intercellular Adhesion Molecule-1) and VCAM-1 (Vascular Cell Adhesion Molecule-1), which mediate leukocyte recruitment and amplify vascular damage [33]. Through the reduction in ROS levels, nanocatalysts reduce endothelial activation, thus creating a more favorable microenvironment for tissue regeneration. The microenvironment modulation supports vascular integrity and maintains microcirculation, a prerequisite for proper tissue perfusion [34].

Experimental evidence supports the beneficial effects of nanocatalysts on the preservation of endothelial function, showing improved vascular reactivity, reduced oxidative tissue damage, and accelerated endothelial repair in models of ischemic injury [35]. These results explain the therapeutic potential of such nanoparticles in diseases related to endothelial dysfunction, including microvascular hypertension, angiogenic alterations, and other vascular diseases.

Cerium Oxide Nanoparticles

The cerium oxide (CeO_2) nanoparticles have been reported to show quite different behaviors in fighting oxidative stress [18,19]. This event occurs at the particle surface and has been shown to mimic the action of antioxidant enzymes. In the Ce^{3+} state, these nanoparticles donate electrons to neutralize superoxide anions ($O_2\bullet^-$), while in the Ce^{4+} state, they accept electrons to decompose hydrogen peroxide (H_2O_2) into water and oxygen, like the effect of iron oxide nanoparticles. This occurs both at the cellular membrane, where lipids are especially prone to peroxidation, and in the nucleus, where DNA oxidation is prevented. This neutralization of free radicals is especially important in tissues sensitive to ischemia-reperfusion injury, as in tissues after vascular damage, where a rise in ROS production can cause further cellular damage.

The main application of cerium oxide in the nanocatalysis field stems from its unique properties compared to other materials. Ceria (CeO_2), especially in a nano form, is an exceptional material for two reasons: (i) they can undergo a reduction of Ce^{4+} to Ce^{+3} oxidation state without structural changes while maintaining their characteristic cubic structure [36,37]; (ii) they promote a rapid transport of oxygen through the lattice [38]. Also, cerium oxide or yttrium oxide nanoparticles protect nerve cells from oxidative stress, and the neuroprotection is independent of particle size. These nanoparticles act as direct antioxidants to limit the amount of ROS required to kill the cells [39]. Recently, the biochemical properties of cerium oxide have been explored [40-46]. Nanoceria may act as antioxidants, protect cells against oxidative damage and ionizing radiation, improve cardiac function, and induce oxidative stress [46]. This research focused on the redox capability of nanoceria reacting with ROS and evaluated the cellular responses in oxidative

stress conditions. Under normal conditions, the response of cells to nanoceria exposure remains unknown. Naked nanoceria could act as antioxidants to protect cells against oxidative damage. While the redox properties may be beneficial, the genome-wide effects of nanoceria on gene transcription and associated biological processes remain elusive [47]. Other potential nano-oxides for medicinal applications are Mn, Cu, and Fe oxides, which can have valencies similar to Ce [48-50]. A recent paper on a medicinal novel use of nanoparticles reported the development of nanocarrier-based oral pegfilgrastim formulations for mitigating hematopoietic acute radiation syndrome [51]. The molecular mechanism underlying the therapeutic effect of cerium nanoparticles (CeNPs) in oncology has been reported [52]. Cancer cells were treated with different concentrations of pure nanocerium of various sizes and synthesized by laser ablation. Due to oxygen species on the ROS-modulating properties of cerium nanoparticles, the nanoparticles were not coated with surfactants or organic molecules during synthesis, which could potentially inhibit many pro-oxidative effects. ROS production, expression of genes encoding redox-status proteins, and proteins regulating cell death and endoplasmic reticulum stress (ER-stress) were investigated as indicators of the molecular mechanism of cancer cell death. Studies were conducted on the effects of cerium nanoparticles on the Ca^{2+} signaling system of cancer cells of different origins [52]. The study of the chemical and biological properties of CeO_2 nanoparticles (CNPs) has expanded recently due to their therapeutic potential, and the methods used to synthesize these materials are diverse. Moreover, conflicting reports exist regarding the toxicity of CNPs [53].

Recently, a critical review evolved from a Special Workshop on Nanoceria panel presentation addressing the toxicological risks of nanoceria [54]: accumulation, target organs, and issues of clearance; how exposure dose/concentration, exposure route, and experimental preparation/model influence the different reported effects of nanoceria; and how can safer by design concepts be applied to nanoceria. It focuses on the most relevant routes of human nanoceria exposure and uptake, disposition, persistence, and resultant adverse effects. The pulmonary, oral, dermal, and topical ocular exposure routes and the intravenous route are addressed, as the latter provides a reference for the pharmacokinetic fate of nanoceria once introduced into the blood. Nanoceria reaching the blood is primarily distributed to mononuclear phagocytic system organs.

The health assessments of cerium oxide nanoparticles need to include the epidemiology studies of cerium oxide nanoparticles used as automotive diesel fuel additive, aerosol particulate matter in air, and other industrial ultrafine and nanoparticles generated in welding and flame cutting [55]. The synthesis control in obtaining CeO_2 nanostructures is of fundamental importance for obtaining materials with desired properties. However, progress in synthesizing and controlling the properties of these unidirectional (1D) nanomaterials remains a major challenge [56-58]. Alkaline hydrothermal synthesis without using a template was performed under different reaction conditions, and the influence on the morphological, structural, and optical properties of CeO_2 nanotubes (CeNTs) formed was discussed [56]. In some cases, nanosized ceria organized were obtained, with varying sizes and quantities of oxygen vacancies, according to the syntheses' condition, thus generating materials with different properties [57-62].

Conclusions

Catalytic nanomedicine is an emerging strategy that fights oxidative stress by utilizing nanocatalysts that mimic antioxidant enzymes. These nanocatalysts possess unique properties, including high stability and controlled reactivity, granting them the remarkable ability to efficiently and selectively neutralize reactive oxygen species (ROS). Moreover, their capability to be directed to sites of oxidative damage further enhances their potential to address conditions associated with chronic inflammation, cellular aging, and various degenerative diseases. Although considerable progress has been made in this field, several challenges must be addressed, such as the safety of nanocatalysts, their biodistribution in the body, and the scalability of their production. Emphasis is placed on the recent applications of cerium oxide systems in nanomedicine due to their distinct properties compared to other materials. Ceria

(CeO_2), particularly in its nano form, is a noteworthy material for two reasons: (i) it can undergo the reduction of Ce 4^+ to Ce 3^+ oxidation state without structural changes while maintaining its characteristic cubic structure, and (ii) it promotes rapid oxygen transport through the lattice. Cerium oxide nanoparticles (nanoceria) are versatile engineered nanoparticles (ENPs) because of their unique redox properties. These features require further investigation to optimize therapeutic benefits while minimizing risks. Continued investment in such studies is essential for fully realizing the clinical applications of these technologies, maximizing their therapeutic potential, and ultimately translating nanocatalysts into more effective clinical treatments. Control over synthesis parameters can be achieved by managing the nanomaterial's formation, size and varying Ce 4 +/Ce 3 + ratios. This control over the production of these nanostructures, combined with energy gap considerations, may yield differential performances for applications in photocatalysis, sensors, and precision nanomedicine.

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Author contributions

Sofia F. Coriolano Araujo conceived the idea and conducted the literature survey jointly with Rosana A. S. Fonseca and Antonio S. Araujo. They wrote the manuscript, which A.S.A. reviewed and edited.

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